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1: Neurourol Urodyn. 2000; 19(3): 279-87. Related Articles, Links

InterScience

Preliminary results of myoblast injection into the urethra and bladder wall: a possible method for the treatment of stress urinary incontinence and impaired detrusor contractility.

Chancellor MB, Yokoyama T, Tirney S, Mattes CE, Ozawa H, Yoshimura N, de Groat WC, Huard J.

Division of Urologic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

The purpose of this study is to explore the feasibility of myoblasts, the precursors of muscle fibers, injected periurethrally as a potential treatment of stress urinary incontinence. We also studied myoblast injection into the bladder wall to potentially improve detrusor contractility. A myoblast cell line was transduced with adenovirus carrying the expression of the beta-galactosidase reporter gene while in culture. The cells were incubated with fluorescent latex microspheres (FLMs) to follow the outcome of the injected cells. The tissue was harvested 3-4 days after injection; sectioned, fixed, assayed for beta-galactosidase expression, and counterstained with H+E. Photographs of the slides were taken under light and fluorescence microscopy. We have noted a large number of cells expressing beta-galactosidase and containing FLMs in the urethral and bladder walls under fluorescent microscopy (8 animals). Many regenerative myofibers expressing beta-galactosidase were also seen in the urethral and bladder walls. The fusion of injected myoblasts to form myotubes was seen in both the urethral and bladder walls. The introduction of myoblasts into the urethral and bladder wall is feasible and results in formation of myotubes and myofibers in the smooth muscle layers of the lower urinary tract. We hypothesize that myoblast injections can be used as a non-allergenic agent to enhance urethral closure and bladder function.

PMID: 10797585 [PubMed - indexed for MEDLINE]

2: J Urol. 2001 Jan; 165(1): 271-6. Related Articles, Links

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Persistence and survival of autologous muscle derived cells versus bovine collagen as potential treatment of stress urinary incontinence.

Yokoyama T, Yoshimura N, Dhir R, Qu Z, Fraser MO, Kumon H, de Groat WC, Huard J, Chancellor MB.

Departments of Urology, Pharmacology, Orthopedic Surgery and Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

PURPOSE: We explored the use of autologous muscle derived cells as a method of treating stress urinary incontinence. We determined whether urethral muscle derived cell injection is feasible and compared it with bovine collagen injection. MATERIALS AND METHODS: Muscle derived cells isolated from female Sprague-Dawley rats were first transduced with retrovirus carrying the

transgene for beta-galactosidase. We injected approximately 1 to 1.5 x 106 cells into the bladder wall and proximal urethra of 6 autologous animals. Tissue was harvested after 3 and 30 days, sectioned, stained for fast myosin heavy chain and assayed for beta-galactosidase. To compare muscle derived cell and bovine collagen injections 100 microl. of commercially available bovine collagen were also injected in Sprague-Dawley female rats. Tissue was harvested in 3 animals each after 3 and 30 days, sectioned and stained for trichrome. Subsequently, 3 adult SCID mice were used to compare the level of transgene expression at each time point after injecting 1.5 x 106 cells per injection, which were transduced with adenovirus carrying the transgene for beta-galactosidase. RESULTS: A large number of cells expressing beta-galactosidase were observed in the bladder and urethral wall 3 and 30 days after autologous cell injection in Sprague-Dawley rats. The persistence of primary muscle derived cells at 3 days was similar to that of collagen. However, at 30 days there was significant cell persistence while only a minimal amount of injected bovine collagen was detectable. Approximately 88% of the beta-galactosidase expression at day 3 remained at day 30 in SCID mice. CONCLUSIONS: We present 2 new findings important for the emerging field of urological tissue engineering, including the feasibility of injecting autologous skeletal muscle derived cells into the lower urinary tract and the greater persistence of such injected cells versus injected bovine collagen. Therefore, autologous muscle derived cell injection may be an attractive alternative treatment option for stress urinary incontinence.

PMID: 11125423 [PubMed - indexed for MEDLINE]

☐ 3: Urology. 2001 Apr; 57(4): 826-31. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Muscle-derived cell transplantation and differentiation into lower urinary tract smooth muscle.

Yokoyama T, Huard J, Pruchnic R, Yoshimura N, Qu Z, Cao B, de Groat WC, Kumon H, Chancellor MB.

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

OBJECTIVES: To explore the feasibility of primary skeletal muscle-derived cell (MDC)-based tissue engineering and gene transfer into the lower urinary tract and to explore whether the injected primary skeletal MDCs can persist and differentiate into myotubes and myofibers in the bladder wall. METHODS: Primary MDCs isolated from normal mice were first transduced with adenovirus encoding the expression of the beta-galactosidase reporter gene. Adult severe combined immunodeficiency mice (n = 12) were used in this study. The MDCs were injected into the right and left lateral bladder walls with a 10-microL Hamilton microsyringe. The amount of injected MDCs ranged from 1 to 1.5 x 10(6) cells. The tissue was harvested after 5, 35, and 70 days, sectioned, stained for fast myosin heavy chain, and assayed for beta-galactosidase expression. RESULTS: We observed a large number of cells expressing beta-galactosidase in the bladder wall at each time point. Many myotubes and myofibers expressing beta-galactosidase and positively stained for fast myosin heavy chain were also seen in the bladder wall at 35 and 70 days after injection. Additionally, the size of the injected MDCs significantly increased during the course of the study ($P < 0.05$). CONCLUSIONS: We have demonstrated the long-term survival and beta-galactosidase expression of MDCs injected into the bladder wall. Moreover, our results suggest that some injected MDCs can differentiate into myofibers. These results suggest that MDCs can be a desirable substance for tissue engineering and an ex vivo method for gene transfer into the lower urinary tract.

PMID: 11306423 [PubMed - indexed for MEDLINE]

☐ 4: Gene Ther. 2002 Dec; 9(23): 1617-26. Related Articles, Links

nature publishing group

Muscle-derived cell-mediated ex vivo gene therapy for urological dysfunction.

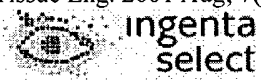
Huard J, Yokoyama T, Pruchnic R, Qu Z, Li Y, Lee JY, Somogyi GT, de Groat WC, Chancellor MB.

Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

We have tested the feasibility of muscle-based gene therapy and tissue engineering for urological dysfunction using highly purified muscle-derived cells (MDC) that display stem cell characteristics. We then explored the potential use of these MDC as an alternative therapy for the treatment of impaired detrusor contractility. The MDC were genetically engineered to express the gene encoding beta-galactosidase and injected into the bladder walls of SCID mice. The injected bladders were harvested at various time-points after injection and assayed for beta-galactosidase activity; the presence of myofibers within the injected tissue was determined by detection of fast myosin heavy chain isoform (MyHCs). We have demonstrated that the injected MDC are capable of not only surviving in the lower urinary tract, but also improving the contractility of the bladder following an induced injury. Two potential mechanisms can be used to explain this finding. First, we have observed that some of the beta-galactosidase-expressing cells expressed alpha-smooth muscle actin, suggesting a differentiation into smooth muscle. Second, a stain for acetylcholine receptors (AChRs), which identifies the location of neuromuscular junctions, revealed that the myofibers derived from the doner cells became innervated into the bladder as early as 2 weeks after injection. These results suggest that gene therapy and tissue engineering based on MDC potentially can be used for urological dysfunction.

PMID: 12424614 [PubMed - indexed for MEDLINE]

☐ 5: Tissue Eng. 2001 Aug; 7(4): 395-404. Related Articles, Links



Autologous primary muscle-derived cells transfer into the lower urinary tract.

Yokoyama T, Pruchnic R, Lee JY, Chuang YC, Jumon H, Yoshimura N, de Groat WC, Huard J, Chancellor MB.

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

The goal of these experiments was to establish the basic methodology for future clinical applications of muscle-derived cells (MDC) tissue engineering and gene transfer for the treatment of urological dysfunction. Primary MDC isolated via preplating techniques from adult female SD rats were transduced with retrovirus encoding the expression of beta-galactosidase reporter gene. The MDC were injected into the right and left lateral walls of the bladder and proximal urethra of the autologous animals (n = 6) with a 10 microl Hamilton micro syringe. The amount of injected MDC ranged from 1 to 2 x 10(6) cells. The injected tissue was harvested after 7, 14, and 28 days, sectioned and examined histologically for beta-galactosidase and immunohistochemically for fast myosin heavy chain specific to skeletal muscle. The tissues were also stained for anti-CD4 and anti-CD8 antibodies to assess for cellular immune reaction. We have detected a large number of autologous MDC expressing beta-galactosidase and positively stained for fast myosin heavy chain in the bladder and urethral wall. Many injected myoblasts and myotubes were also seen in the bladder and urethral wall at each time point. Staining of lymphocytes with anti-CD4 and anti-CD8 antibodies was negative after MDC injection at each time point. We have demonstrated the long-term survival of autologous MDC and MDC mediated gene transfer into the bladder and urethral wall. Autologous MDC and MDC mediated gene transfer may be a promising treatment to augment bladder and urethral sphincter function.

PMID: 11506729 [PubMed - indexed for MEDLINE]

☐ 6: Muscle Nerve. 1994 Sep; 17(9): 975-80. Related Articles, Links

Utilization of myoblasts from transgenic mice to evaluate the efficacy of myoblast transplantation.

Kinoshita I, Huard J, Tremblay JP.

Laboratoire de Neurobiologie, Universite Laval, Hopital de l'Enfant-Jesus, Quebec, Canada.

A possible treatment for Duchenne muscular dystrophy is the injection of normal myoblasts into dystrophic muscles to induce the formation of new, healthy, and dystrophin-positive muscle fibers. To develop this therapy, it is important to identify the muscle fibers formed by the injected myoblasts in the host muscles. In this study, we used myoblasts from transgenic mice which have a gene expressing beta-galactosidase under the control of the promoter of quail fast skeletal muscle troponin I. This transgene is expressed in myotubes and muscle fibers, but not in myoblasts. Twenty-eight days after myoblast transplantation in nude and in mdx mice, muscle fibers containing of beta-galactosidase were identified by x-gal staining. In mdx mice, most of the beta-galactosidase-positive muscle fibers resulting from the myoblast transplantation were also dystrophin positive. This technique could make it possible to follow the success of myoblast transplantation even in mice that are not depleted of dystrophin.

PMID: 8065399 [PubMed - indexed for MEDLINE]

☐ 7: World J Urol. 2000 Feb; 18(1): 56-61. Related Articles, Links

Myoblast therapy for stress urinary incontinence and bladder dysfunction.

Yokoyama T, Huard J, Chancellor MB.

Division of Urologic Surgery, University of Pittsburgh School of Medicine, Pennsylvania, USA.

The field of tissue engineering and gene therapy has an exciting and promising future. During the past few years we have begun a comprehensive effort to investigate the use of myoblasts to improve and expand the treatment of stress urinary incontinence and bladder dysfunction. Moreover, we can expect the application of myoblast-mediated ex vivo gene transfer in the field of urology. In this paper we discuss the compositions of and methods involving the use of myogenic or muscle-derived cells for tissue engineering and cell-mediated gene therapy.

PMID: 10766045 [PubMed - indexed for MEDLINE]

☐ 8: J Urol. 1999 Jul; 162(1): 204-12. Related Articles, Links

Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability.

Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, Chancellor MB.

Department of Pharmacology, University of Pittsburgh School of Medicine, Pennsylvania, USA.

PURPOSE: A causative relationship between stress urinary incontinence (SUI) and detrusor instability has been suspected but never proven. Many women with mixed incontinence have resolution of detrusor instability after surgical correction of SUI. We sought experimental support that stimulation of urethral afferent nerves can induce or change reflex detrusor contractions. MATERIALS AND METHODS: Urethral perfusion pressure and isovolumetric bladder pressure were measured with catheters inserted through the bladder dome in urethane anesthetized female S.D. rats (250 to 300 grams; n = 12). The catheter assembly was seated securely in the bladder neck to block passage of fluid between the bladder and urethra without affecting the nerve supply to the

organs. The external urethra was not catheterized. Responses were examined in the control state at a urethral saline perfusion speed of 0.075 ml. per minute. Intraurethral drugs were administered following blockade of striated sphincter activity with intravenous alpha-bungarotoxin (0.1 mg./kg.). RESULTS: Stopping the urethral saline infusion caused a significant decrease in micturition frequency in approximately 50% of the animals studied (n = 12). Intraurethral lidocaine (1%) infused at 0.075 ml. per minute caused a slight decrease in urethral perfusion pressure but no change in detrusor contraction amplitude. However, intraurethral lidocaine caused a significant (45%) decrease in the bladder contraction frequency (n = 5). The micturition frequency returned to baseline 30 minutes after stopping lidocaine infusion. Intraurethral infusion of nitric oxide (NO) donors (S-nitroso-N-acetylpenicillamine [SNAP] (2 mM) or nitroprusside (1 mM) immediately decreased urethral perfusion pressure by 30 to 37% (n = 5). A 45 to 75% decrease (n = 5) in bladder contraction frequency was also seen, which was similar to that observed following lidocaine. Neither NO donor changed the amplitude of bladder contractions. CONCLUSIONS: These results indicate that in the anesthetized rat activation of urethral afferents by urethral perfusion can modulate the micturition reflex. Thus in patients with stress urinary incontinence, leakage of urine into the proximal urethra may stimulate urethral afferents and facilitate voiding reflexes. This implies that stress incontinence can induce and/or increase detrusor instability. These findings have significant implications for the treatment of patients with mixed urge and stress incontinence. Correction of stress incontinence by surgery or pelvic floor exercise in patients with mixed incontinence may resolve the detrusor instability.

PMID: 10379788 [PubMed - indexed for MEDLINE]

9: Urology. 2003 Nov; 62(5): 958-63. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Improved sphincter contractility after allogenic muscle-derived progenitor cell injection into the denervated rat urethra.

Cannon TW, Lee JY, Somogyi G, Pruchnic R, Smith CP, Huard J, Chancellor MB.

Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

OBJECTIVES: To study the physiologic outcome of allogenic transplant of muscle-derived progenitor cells (MDPCs) in the denervated female rat urethra. METHODS: MDPCs were isolated from muscle biopsies of normal 6-week-old Sprague-Dawley rats and purified using the preplate technique. Sciatic nerve-transected rats were used as a model of stress urinary incontinence. The experimental group was divided into three subgroups: control, denervated plus 20 microL saline injection, and denervated plus allogenic MDPCs (1 to 1.5 x 10(6) cells) injection. Two weeks after injection, urethral muscle strips were prepared and underwent electrical field stimulation. The pharmacologic effects of d-tubocurare, phentolamine, and tetrodotoxin on the urethral strips were assessed by contractions induced by electrical field stimulation. The urethral tissues also underwent immunohistochemical staining for fast myosin heavy chain and CD4-activated lymphocytes. RESULTS: Urethral denervation resulted in a significant decrease of the maximal fast-twitch muscle contraction amplitude to only 8.77% of the normal urethra and partial impairment of smooth muscle contractility. Injection of MDPCs into the denervated sphincter significantly improved the fast-twitch muscle contraction amplitude to 87.02% of normal animals. Immunohistochemistry revealed a large amount of new skeletal muscle fiber formation at the injection site of the urethra with minimal inflammation. CD4 staining showed minimal lymphocyte infiltration around the MDPC injection sites. CONCLUSIONS: Urethral denervation resulted in near-total abolishment of the skeletal muscle and partial impairment of smooth muscle contractility. Allogenic MDPCs survived 2 weeks in sciatic nerve-transected urethra with minimal inflammation. This is the first report of the restoration of deficient urethral sphincter function through muscle-derived progenitor cell tissue engineering. MDPC-mediated cellular urethral myoplasty warrants additional investigation as a new method to treat stress urinary incontinence.

Publication Types:
- Evaluation Studies

PMID: 14624934 [PubMed - indexed for MEDLINE]

5: Br J Urol. 1993 Nov; 72(5 Pt 1): 559-65. Related Articles, Links

Bladder contractility and idiopathic detrusor instability in the female.

Cucchi A.

Divisione di Urologia, Policlinico S. Matteo, Pavia, Italy.

Twenty females with pure stress urinary incontinence (Group A) were studied clinically and urodynamically together with 20 stress incontinent women with idiopathic detrusor instability (Group B) and 20 controls (Group C). Forty females with the idiopathic urge syndrome, 20 with detrusor instability (motor urgency, Group D) and 20 with stable bladders (sensory urgency, Group E) were also investigated. Detrusor contractility, assessed on the basis of strength and velocity parameters derived from pressure flow data, was increased in the unstable groups. In particular, the maximum mechanical power (per unit of bladder wall surface area) generated by the contracting detrusor during voiding was higher in the unstable patients, this was also the case when estimating maximum bladder contraction velocity. No significant difference in these parameters was found in the patients with sensory urgency when compared with the controls and with the women with stress urinary incontinence, nor was there any significant difference between patients with motor urgency and the stress incontinent patients with detrusor instability. The enhanced contractile capability could be explained in the unstable stress incontinent group by a reduced threshold of stretch receptors in the urethral walls. If this were the case, urine running through the urethra at the beginning of voiding would be able to activate a urethrovesical reflex which may augment micturition contractions. In the group with the idiopathic urge syndrome one could speculate that sensory and motor urgency are due to the same neurological disorder (i.e. possibly a reduction in a tonic inhibitory or modulatory device) that would affect detrusor mechanics at different levels of the nervous system, resulting in different contractile capabilities.

PMID: 10071537 [PubMed - indexed for MEDLINE]

6: Ceska Gynekol. 1998 Jun; 63(3): 199-202. Related Articles, Links

[Ultrasonography of pelvic floor muscles in women with urinary stress incontinence]

[Article in Czech]

Masata J, Martan A, Halaska M, Voigt R, Drbohlav P.

I. gynek.-porod. klinika 1. LF UK a VFN, Praha.

Ultrasound examinations have become since beginning of the eighties one of the auxiliary examination methods in urogynaecology. Evaluation of the position and mobility of the neck of the urinary bladder practically replaced lateral chain urethrocystography. With the improving differentiating capacity of ultrasound equipment it is possible to visualize some periurethral and paravaginal structures which participate in the support of the urethra and urethrovesical junction by paravaginal and periurethral structures in women (fig. 1). In recent years many papers were published where for visualization nuclear magnetic resonance (NMR) is used [1, 12, 19]. The functional and physiological condition of these tissues is assessed by physical, urodynamic and ultrasonographic examinations and also by cystourethroscopy and manometry [7, 11, 10, 13, 14, 15, 16]. Despite this the greater part of anatomical knowledge of the supporting apparatus is derived from pathological studies and peroperative observations.

PMID: 9750380 [PubMed - indexed for MEDLINE]

7: Acta Obstet Gynecol Scand. 1993 Nov; 72(8): 661-7. Related Articles, Links

Tests for 'detrusor instability' in women. These mainly measure the urethral resistance created by pelvic floor contraction acting against a premature activation of the micturition reflex.

Petros PE, Ulmsten U.

Department of Gynecology, Royal Perth Hospital, Western Australia.

The principal aim of this study was to analyse the simultaneous pressure readings derived from bladder and urethra during a handwashing test. A total of 163 patients with urinary incontinence were studied. It was demonstrated that contraction of the pelvic floor stretches the vagina. In many patients, this appeared to inhibit the micturition reflex, possibly by supporting the nerve endings at bladder neck, thereby inhibiting their

☐ 10: Am J Obstet Gynecol. 2000 Apr; 182(4): 879-84. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Ultrastructure of detrusor and urethral smooth muscle in women with urinary incontinence.

FitzGerald MP, Russell B, Hale D, Benson JT, Brubaker L.

Section of Urogynecology and Reconstructive Pelvic Surgery, Department of Obstetrics and Gynecology, Rush Medical College, Chicago, Illinois, USA.

OBJECTIVE: We performed a quantitative study to determine whether mixed urinary incontinence was associated with any ultrastructural changes in detrusor and urethral smooth muscle. STUDY DESIGN: Detrusor and urethral smooth muscle biopsy specimens were obtained at the time of laparotomy from 5 women aged 35 to 65 years with mixed urinary incontinence and from a control group of 5 continent women. Smooth muscle morphologic characteristics were assessed from a systematic random sample of electron micrographs. A further 16 urethral biopsy specimens were similarly analyzed to confirm the findings of the initial study. RESULTS: The electron-dense portion of the sarcolemma was smaller in urethral biopsy specimens taken from patients with intrinsic sphincter deficiency than in those from control subjects (chi(2)((1)) = 4.9; P =.027). No other morphologic characteristics were unique to patients with incontinence. CONCLUSIONS: Our study suggests that focal adhesion architecture is decreased in urethral smooth muscle of patients with intrinsic sphincter deficiency.

PMID: 10764466 [PubMed - indexed for MEDLINE]